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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,889	10/20/2000	Yair Feld	00/20989	7655

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/691,889	FELD ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,24,28-33,35,40,42-46,48-52,54-56 and 59-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,28-33,35,40,42-46,48-52,54-56 and 59-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed October 28, 2005 (hereinafter referred to as "the response") has been entered. Claims 32, 45, and 51 have been amended. Claims 61-83 have been newly added.

Accordingly, Claims 23, 24, 28-33, 35, 40, 42-46, 48-52, 54-56, and 59-83 are pending in the instant application.

The rejection of Claims 23, 24, 28-33, 35, 40, 42-46, 48-52, and 54-60 under 35 U.S.C. 103(a) is withdrawn in view of the Declaration of Dr. Feld under 37 CFR 1.131, stating that the present invention was reduced to practice prior to the effective September 6, 2000 filing date of Donahue et al. (U.S. Patent Application No. 2004/0266717).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23, 24, 28-33, 35, 40, 42-46, 48-52, 54-56, and 59-83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 23-37 of copending Application No. 10/399,715. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are fully encompassed by the claims of the copending application. Although the claims of the copending application cover *in vivo* gene transfer, *ex vivo* gene transfer, as well as the engraftment of cells that are not genetically modified, the instant claims, directed to *ex vivo* gene transfer, are obvious over the claims of Application No. 10/399,715, given that the copending claims cover *ex vivo* gene transfer, which is a very substantial scope of the claims. Furthermore, both sets of claims cover the use of a polynucleotide encoding any ion channel or any transporter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 24, 28-33, 35, 40, 42-46, 48-52, 54-56, and 59-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

Enablement has been evaluated giving due consideration to all the Wands factors, and the following factors are particularly noteworthy:

Nature of the Invention and Scope of the Claims. The claims are directed to a method of modifying the electrophysiological function of an excitable tissue region of an individual, the method comprising: (a) providing cells expressing an exogenous polypeptide forming a functional ion channel or transporter; and

(b) implanting said cells into the excitable tissue region, such that each implanted cell forms:

(i) gap junctions with at least one cell of the excitable tissue region; and

(ii) a functional ion channel or transporter;

thereby modifying the electrophysiological function of the excitable tissue region, wherein expression of said exogenous polypeptide is regulatable by an endogenous or an exogenous factor. All claims are directed to *ex vivo* gene therapy. Claims 33, 46, 52, 55, 56, 64-67, 71, 75, 79, and 83 recite that the method is utilized for regulating cardiac arrhythmia. Various claims (e.g., Claim 35) recite that the method is utilized for regulating neuronal discharge. The specification asserts that the present invention

(*i.e.*, the method of *ex vivo* gene therapy) can be used for restoring normal electrophysiological function to damaged tissues such as heart, nerve, or glandular tissues (page 9, lines 4-7). Thus, the nature of the invention relates to treatment of patients having a variety of deficits in excitable tissues. The claims are broad in scope, encompassing treatment of a wide variety of diseases and disorders, including epilepsy, diabetes, Parkinson's disease, and cardiac arrhythmias. Thus, the claimed method encompasses treatment of a wide variety of disorders. The specification does not assert any use, other than treatment, for the claimed method of *ex vivo* gene therapy.

The specification contemplates that the method of the invention can be applied to treat a variety of cardiac arrhythmias (page 58, lines 17-18). The specification further contemplates that astrocytes transfected with selected ion channels may be used to modulate focal pathological areas in the central nervous system (CNS), thus enabling treatment of disorders such as epilepsy, Parkinson and the like (page 59, lines 18-21). Thus, the claims encompass treatment of a huge variety of diseases of the CNS. Furthermore, the claims are very broad in scope with regard to the type of therapeutic effect to be achieved by the method (e.g., regulating neuronal discharge, regulating cardiac arrhythmia, rhythm control for atrial fibrillation). All claims are presently drawn to *ex vivo* gene therapy, wherein the implanted cell is transformed prior to transplantation. Moreover, the claimed method covers the use of any cell type and any ion channel or transporter.

The only utility asserted in the specification for the claimed method is to produce a therapeutic effect. Thus, the claims are directed to *ex vivo* gene therapy methods of considerable breadth.

Amount of direction or guidance presented and the presence or absence of working examples. The teachings of the specification are limited to analysis of conduction properties of cells in cultures in a variety of assays (Example 5, pages 50-59). In Example 5, the electrical properties of fibroblasts transfected with the Kv1.3 channel coding sequence (Kv1.3 fibroblasts) in co-cultures with unmodified rat ventricular cardiomyocytes were analyzed. The presence of Kv1.3 fibroblasts in co-

culture with cardiomyocytes caused a variety of changes in the electrophysiological function of cardiomyocyte monolayer cultures. The specification does not provide any working examples with regard to treatment of a diseased animal by implantation of cells as recited in the claims. The Declaration of Dr. Feld, filed March 3, 2003, describes experiments where a rat fibroblast cell expressing an exogenous polypeptide Kv1.3 ion channel is implanted into the rat heart (left ventricular free wall or atrio-ventricular junction). The promoter used to drive expression of the Kv1.3 ion channel is not disclosed. The effective refractory period was determined prior to transplantation and 5-7 days following transplantation. The average refractory period of the hearts prior to transplantation was 104 ms and 166 ms following transplantation with Kv1.3 fibroblasts. Application of margatoxin, a specific Kv1.3 channel blocker, caused the refractory period to decrease to 130 ms in the transfected group, while no change was seen in the non-transfected group. Thus, it was concluded that the electrophysiological modulation of the cardiac tissue was mediated by Kv1.3. The animals used in the experiments were healthy animals and therefore no treatment effect was noted.

With regard to *ex vivo* gene therapy the specification provides only limited and general guidance for the treatment of a few diseases, including epilepsy, diabetes, and cardiac arrhythmias. The specification fails to provide any **specific guidance** on the generation of the nucleic acid construct to be used in the gene therapy method for the treatment of any specific disease or disorder. Only general guidance is provided.

State of the prior art and predictability of the art. At the time of the invention, successful implementation of *ex vivo* gene therapy protocols was not routinely achievable by those skilled in the art. This is reflected in numerous references. With particular regard to the treatment of cardiac arrhythmias, Donahue et al. (2005a) reports that "[t]he investigation of gene therapeutic strategies to treat cardiac arrhythmias is in its infancy" (page 221, column 1, paragraph 2) and "[a]rrhythmia gene therapy is a field in its infancy, and future human applications are dependent on solutions to the problems discussed in this

review" (abstract). The authors also note several examples of cardiac arrhythmia ion channel gene therapy experiments in animal models and state that "[i]t should be noted for all these examples, and indeed for the field as a whole, that the pathophysiology of arrhythmias is extremely complex" (page 222, column 1, paragraph 2) and "[w]hen dealing with situations of this complexity, surprises will undoubtedly occur as the cardiac system adapts to the therapeutic intervention" (page 222, column 1, paragraph 2). The authors also point out that "[c]urrent problems in the field of gene therapy include ... the inability to control the duration and level of gene expression" (page 222, column 3, paragraph 1). Thus, it is evident that, given the instantly claimed method, success of the protocol is critically dependent on matching a given disease with an appropriate therapeutic construct and an appropriate cell type. The appropriate therapeutic construct must be made by judicious selection of an appropriate promoter, along with other genetic control elements, and an appropriate ion channel gene (or transporter) to effect the desired therapy in the tissue of interest. The construct must then be transfected into an appropriate cell type, such that the particular combination of the various parameters leads to the desired therapeutic result. Although considerable experimental data is available on the function of various ion channels, particularly in neurons, reports suggest that "several tens of different ion channel types are present at the surface membrane and inside the presynaptic nerve terminal" (Meir et al., page 1020, column 1, paragraph 2) and that "[t]he number of different ion channel molecules is probably well over a hundred" (Meir et al., page 1020, column 1, paragraph 2). Given the very broad scope of the claims, development of a therapeutic protocol within the scope of the claims would require undue experimentation.

The instant specification fails to provide sufficient guidance to the skilled artisan to produce a treatment effect across the full scope of the claims, or even for particular embodiments contemplated in the specification. Numerous factors complicate the gene delivery art which cannot be overcome by routine experimentation. These include the *in vivo* consequences of altered gene expression and protein function, the level of mRNA produced, the amount and stability of the protein produced, and the protein's

compartmentalization within the cell, or its secretory fate, once produced. In the instant application, the specification provides little specific guidance with regard to the generation of a nucleic acid construct to be used in an *ex vivo* gene therapy method for the various diseases to be treated. In the absence of specific guidance, the skilled artisan would have been required to develop successful protocols for practicing the claimed methods over a very large and improbable scope, without guidance on a starting point or the direction in which experimentation should proceed. However, given that the *ex vivo* gene therapy art was considered highly unpredictable, the skilled artisan would have been required to engage in undue experimentation to come up with successful gene therapy protocols. Even in the field of cardiac arrhythmias, despite intensive effort on the research front, the existence of successful gene therapy treatment protocols was extremely limited in 2000.

Tomaselli et al. (2003) report that:

> "Direct and indirect gene transfer is an important tool in the study of normal and pathologic cardiac electrophysiology. The use of gene transfer in clinical therapeutics remains intellectually appealing but is subject to a number of substantial challenges before implementation in humans can be considered. These challenges are relevant to gene therapy generically and to the treatment of cardiac arrhythmias specifically." (page 549, column 2, paragraph 2).

and further that:

> "Problems that are more specific to gene therapy for cardiac arrhythmias are exemplified by, but not limited to, our lack of understanding of the molecular mechanisms of many arrhythmias and the spatial complexity of expression of ion channels, which curbs the utility of transfer of a single ion channel species." (page 549, column 2, paragraph 4).

Although *ex vivo* gene therapy approaches to improve automaticity are being developed, Donahue et al. (2005b) reports that "[o]verall, gene transfer approaches to increase cardiac automaticity are in early stages of development" (page 159, paragraph 4) and that "[o]ngoing work in this field has the potential for tremendous impact if the correct gene or combination of genes is identified to allow recreation of true pacemaker activity" (page 159, paragraph 4).

In an article published well after the filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far ..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pages 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of genetic constructs to treat a wide variety of diseases. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation. Rather, the prior art shows that intensive investigation has met with limited success.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims.

The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the unpredictability in the *ex vivo* gene therapy art, and further given that the specification fails to provide specific guidance on which nucleic acids encoding which protein can be used to treat a specific disease of interest, across the very broad scope, the skilled artisan would have been required to engage in undue experimentation to develop a method within the scope of the claims for treating any particular disease.

Given the limited examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon application of the claimed method, the very broad scope of the claims, and the unpredictability for producing a therapeutic effect upon implantation of a genetically modified cell, undue experimentation would have been required for one skilled in the art to develop a protocol within the scope of the claims for treating a wide variety of diseases, and moreover to develop protocols across the full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64-83 are indefinite in their recitation of "said cells" because the term has ambiguous antecedent basis. The independent claims (Claims 23, 28, 29 or 33) each recite an "implanted cell" and "at least one cell of the excitable tissue region," in essence, a donor cell and a host cell. Thus, the later

recitation of "said cells" has ambiguous antecedent basis because it may refer to the donor cell or the host cell.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

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